

## REMARKS

Claims 21-40 are pending. Claims 21, 28, 29, 34-38, and 40 are under examination, and claims 22-27, 30-33, and 39 are withdrawn as being directed to non-elected subject matter. All claims stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 21 and 34-38 stand further rejected under 35 U.S.C. § 102(b) as being anticipated by Levy et al., WO 02/14349 (“Levy”).

### **Claim Amendments**

Claims 21 and 28 are currently amended, and new claims 41-42 are introduced. Claim 21 now recites that the claimed compounds are

“characterized in that one or more radicals, selected from –COOH, –CH(COOH)<sub>2</sub>, –SO<sub>2</sub>H, NH<sub>2</sub>, an amidino, hydroxyamidino, amidrazono, or guanidino group, or a salt thereof, are present in the radicals R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>5</sub>...”

Support for this amendment is found, for example, in previously presented claims 21 and 32. Claim 28 is amended to correct typographical errors in the recited groups “CH<sub>2</sub>,” “NH<sub>2</sub>,” “CH<sub>2</sub>NH<sub>2</sub>,” and “R<sub>5</sub>.” New claim 41 is directed to the compounds of claim 21 where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>5</sub> do not include a charged radical, and new claim 42 is directed to compounds of claim 21 where these groups do include a charged radical. Support for these claims is found, for example, in previously presented claim 21.

No new matter is added by these amendments.

### **Claim Rejection under 35 U.S.C. § 112, Second Paragraph**

Claims 21, 28, 29, 34-38, and 40 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. The Office asserts that the following feature recited in the claims is unclear: “[the compounds are] characterized in that one or more charged radicals, derived

from  $\text{-COOH}$ ,  $\text{-CH(COOH)}_2$ ,  $\text{-SO}_2\text{H}$ ,  $\text{NH}_2$ , an amidino, hydroxyamidino, amidrazono, or guanidino group, are present in the radicals  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$  or  $\text{R}_5$ .” The Office asserts that

- (1) it is unclear what the structures of the encompassed groups are;
- (2) it is unclear whether a particular functional group meets the “charged” limitation if it can be transiently charged or permanently charged; and
- (3) if Applicants intend to claim transiently charged compounds, no conditions are specified and it is impossible to determine whether any particular functional group meets this limitation.

In response to the Office’s assertions, Applicants have amended claim 21 for clarity, and this claim now recites that the claimed compounds are:

“characterized in that one or more radicals, selected from  $\text{-COOH}$ ,  $\text{-CH(COOH)}_2$ ,  $\text{-SO}_2\text{H}$ ,  $\text{NH}_2$ , an amidino, hydroxyamidino, amidrazono, or guanidino group, or a salt thereof, are present in the radicals  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$  or  $\text{R}_5$ ....”

Accordingly, a skilled artisan would understand that compounds encompassed by the instant claims are those where at least one of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ , and  $\text{R}_5$  includes a group selected from

- (a)  $\text{-COOH}$ ,  $\text{-CH(COOH)}_2$ ,  $\text{-SO}_2\text{H}$ ,  $\text{NH}_2$ , an amidino, hydroxyamidino, amidrazono, or guanidino;
- (b) a charged radical that is the conjugate base of  $\text{-COOH}$ ,  $\text{-CH(COOH)}_2$ , or  $\text{-SO}_2\text{H}$ ; and
- (c) a charged radical that is the conjugate acid of any  $\text{NH}_2$ , amidino, hydroxyamidino, amidrazono, or guanidino group.

In addition to the guidance provided in the specification (see, e.g., page 20, lines 22-29), a skilled artisan would recognize that the specified functional groups recited in the claims are acidic or basic groups, as well as have the ability to identify the conditions under which such groups would be neutral or ionized.

In light of the present amendments and arguments, Applicants respectfully request that this ground for rejection be withdrawn.

### **Claim Rejection under 35 U.S.C. § 102(b)**

Claims 21 and 34-38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Levy. Applicants respectfully traverse this rejection.

As stated in M.P.E.P. § 2131 (emphasis added):

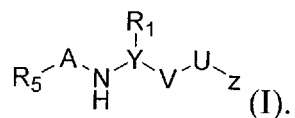
“[w]hen a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art” (citing *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001)).

For a claim to be anticipated under 35 U.S.C. § 102 by a prior art reference, the reference must teach a compound that falls within the claimed genus. Moreover, when a rejection under 35 U.S.C. § 102 is based on inherency,

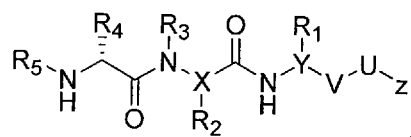
“[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.... ‘[t]o establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient” (M.P.E.P. § 2112(IV)).

Per the guidelines set forth in M.P.E.P. §§ 2112(IV) and 2131, Levy cannot anticipate any of instant claims 21 or 34-38.

The instant claims recite compounds of general formula I, which has the following structure:



Formula I can also be described as follows:

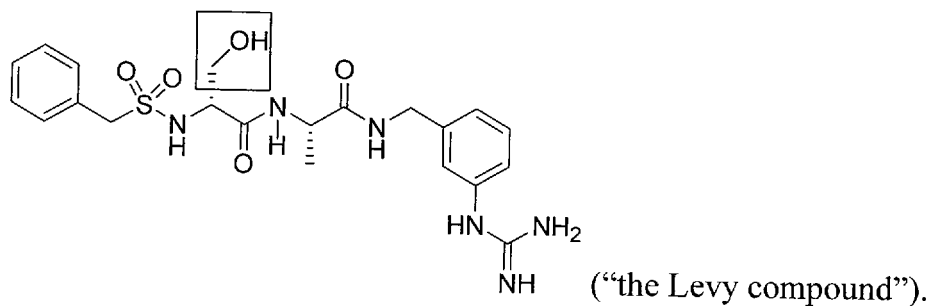


Currently amended claim 21 requires that the claimed compounds of formula I are:

“characterized in that one or more radicals, selected from  $-COOH$ ,  $-CH(COOH)_2$ ,  $-SO_2H$ ,  $NH_2$ , an amidino, hydroxyamidino, amidrazono, or guanidino group, or a salt thereof, are present in the radicals  $R_1, R_2, R_3$  or  $R_5...$ ”

Pursuant to the M.P.E.P. and the case law, any compound that is cited as anticipatory by the Office must satisfy all claimed structural requirements. As shown herein, the Levy reference does not teach any compounds encompassed by the instant claims.

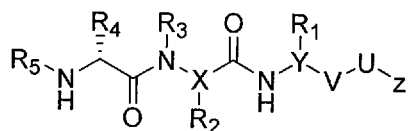
In stating that Levy anticipates instant claims 21 and 34-38, the Office has cited the Levy compound of Example 45,



The Office asserts that, in a solution of  $CF_3CO_2H/CH_2Cl_2$ , the highlighted serine  $-CH_2OH$  group would be protonated and would therefore be encompassed by the instant claims. Levy, however, is completely silent as to the formation of any such protonated species.

Analysis of instant Formula I and the Levy compound shows the following correspondence:

**Corresponding Groups in Instant Formula I:**



$R_1 = \text{H};$

$R_2 = \text{CH}_3;$

$R_3 = \text{H};$

$R_4 = -(\text{CH}_2)_f\text{OR}_{11}$ , where  $f=1$  and  $R_{11}$  is H;

$R_5 = -\text{SO}_2\text{R}_{12}$ , where  $R_{12} =$  unsubstituted aralkyl;

$U = \text{phenyl};$

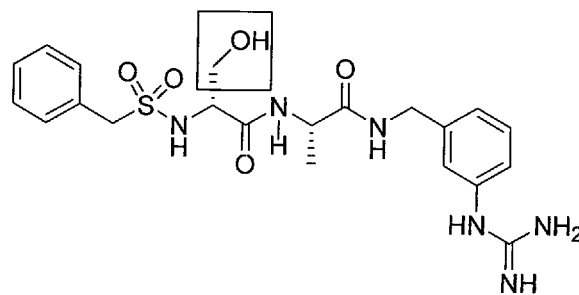
$V = (\text{CH}_2)_n$ , where  $n = 0;$

$X = \text{CH};$

$Y = (\text{CH})_m$ , where  $m = 1;$  and

$Z =$  occurs in the 3-position and is a guanidino group

**The Levy Compound:**



In the Levy compound, the serine  $-\text{CH}_2\text{OH}$  group corresponds to  $R_4$ , and not to any of  $R_1$ ,  $R_2$ ,  $R_3$ , or  $R_5$ . Accordingly, regardless of whether the highlighted hydroxyl group is protonated, none of the structural moieties of the Levy compound corresponds to an allowed group for instant  $R_1$ ,  $R_2$ ,  $R_3$ , or  $R_5$  because none of these moieties includes at least one group selected from  $-\text{COOH}$ ,  $-\text{CH}(\text{COOH})_2$ ,  $-\text{SO}_2\text{H}$ ,  $\text{NH}_2$ , amidino, hydroxyamidino, amidrazono, or guanidino group, or a salt of any of these functional groups. For this reason alone, Levy cannot anticipate the instant claims.

Furthermore, for the record, Applicants respectfully disagree with the Office's assertion that the Levy hydroxyl group would be protonated in the 1:1  $\text{CH}_2\text{Cl}_2/\text{CF}_3\text{CO}_2\text{H}$  solution described in the reference. The respective  $\text{pK}_a$ 's of a protonated serine hydroxyl, i.e., serine- $\text{OH}_2^+$ , and  $\text{CF}_3\text{CO}_2\text{H}$  are  $\sim -2.85$  and  $0.23$ , rendering the protonated serine the stronger acid by two orders of magnitude. Accordingly, the protonation of the Levy hydroxyl group by the trifluoroacetic acid group is thermodynamically unfavorable, and the Office has not provided any scientific evidence to show that protonation of the serine

OH group must occur under these conditions, as required by M.P.E.P. § 2112(IV). Similarly, the Office has provided no basis for the assertion that the serine hydroxyl would be protonated in the stomach (pH ~1-1.5). The Office therefore has not provided the required evidence to support the claim rejection under 35 U.S.C. § 102(b).

In further support of the arguments presented herein, Applicants attach a Declaration by Dr. Andrea Schweinitz, an inventor of the instant application. Dr. Schweinitz, a medicinal chemist and Director of Chemistry at The Medicines Company (Leipzig) GmbH, attests to the facts that the hydroxyl group of the cited Levy compound would not be expected to be protonated in either the trifluoroacetic acid solution described in Levy nor in stomach acid. The § 102 rejection of claim 21 and its dependent claims 34 and 35 should be withdrawn.

Claim 36 is directed to a method of preparing the compound of claim 21. Claims 37 and 38 are directed to pharmaceutical compositions that include the compound of claim 21. Because Levy does not anticipate claim 21, this reference similarly does not anticipate claims 36-38. For these reasons, Applicants also respectfully request withdrawal of this ground for rejection.

### CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Applicants also submit that claim 32, which depends from claim 21, is eligible for rejoinder, and such action is respectfully requested.

Applicants authorize the Office to charge \$52.00 to Deposit Account No. 03-2095 for the fee required by 37 C.F.R. § 1.16(i) in payment of excess claims fees for two (2) excess claims.

Enclosed is a Petition to extend the period for replying to the Office action for one month, to and including April 16, 2010, and payment of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 16, 2010

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